
**Reply to Miceli and Anaissie**

**To the Editor**—We thank Miceli et al. [1] for their response to our article in which they suggest that our observation of an unexpected increase of circulating galactomannan (GM) was due to failure of the infection to respond to caspofungin therapy rather than a paradoxical effect [2]. Our laboratory has >10 years of experience with GM detection in patients with hematological malignancy, and we have not previously observed such high levels of circulating antigen (figure 1). Unlike our patient, the patients described by Maertens et al. [3] received antifungal treatment prior to caspofungin therapy. One study presented by Miceli et al. [1] as evidence of the nonexistence of a paradoxical effect relates to combination antifungal therapy with another echinocandin (micafungin and ravuconazole) in an animal model for invasive aspergillosis (IA) and differs from our patient, who received primary monotherapy with caspofungin [4]. Two other studies mentioned also fail to exclude a paradoxical effect and cannot be compared with our case. First, the kinetics of GM in patients who experience chronic granulomatous disease are known to be different from those in hematological patients [5]. Second, the results by van Vianen et al. [6] have not been consistently found by other researchers. Wiederhold et al. [7] detected an increase in quantitative lung tissue Aspergillus DNA (by RT-PCR) in neutropenic mice with pulmonary aspergillosis after treatment with caspofungin, 4 mg/kg per day, compared with 1 mg/kg per day. Our clinical observation is supported by both an animal model [8] that was not referred to by Miceli et al. [1] and our own in vitro experiment, in which fungal biomass was correlated with the release of GM by the causative Aspergillus strain following exposure to caspofungin [2].

The lack of a consistent description of a paradoxical effect should not provide the
impetus to definitely conclude that an increase and subsequent decrease of GM after administration of caspofungin represents treatment failure. In our patient, this was not the case. An increase and decrease in GM during therapy does not necessarily presage the outcome in one way or another. Our point was that one should exercise caution in interpreting the GM serum ratio in patients who receive caspofungin—or any other antifungal, for that matter.

Acknowledgments

Potential conflicts of interest. P.E.V. has been a consultant for Merck & Company, Gilead Sciences, Schering-Plough, Pfizer, and Vicuron. R.R.K. and J.P.D.: no conflicts.

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References


Illness in Travelers Visiting Friends and Relatives: What Can Be Concluded?

To the Editor—We were interested to read the GeoSentinel report by Leder et al. [1] that focused on an important group of international travelers who, to date, have not been clearly defined in terms of demographic characteristics and travel-related morbidity. We suggest that there are significant issues related to the design, analysis, interpretation, and conclusions of the study that require comment. Although Leder and colleagues acknowledge several limitations in their report, practitioners who are not familiar with the nature of the GeoSentinel program and/or who do not work with migrant travelers may not fully appreciate the significance of these limitations.

First, although the classification of travelers into 3 groups looks appealing, the classifications have been applied retroactively to the data, and the consequences of this are significant. The retrospective cohort nature of the study design limits the interpretation of outcomes to a cohort association and diminishes the generalizability of the conclusions to wider practice outside of the participating GeoSentinel centers.

Second, there is no design evidence that the recategorization of travelers into “immigrant visiting friends and relatives,” “traveler visiting friends and relatives,” and “tourist,” as defined within the report, is either robust or reliably discriminating for travel-related risk or for health outcomes.

Third, the data recruitment allows for the introduction of both patient referral and selection bias. This may create epidemiological associations that may not be representative of travelers outside of the study group. GeoSentinel sites are often academic or tertiary care centers, and are predominantly based in America; thus, they may be biased towards recruiting tourists rather than travelers visiting friends and relatives. Patterns of access to medical service by migrants may differ from those of the host population [2]. Allowable health insurance coverage and issues of willingness to pay for services in the visited nation [3] may influence pretravel and posttravel service use by travelers visiting friends and relatives. Insurance coverage may be linked to the study’s observations of early clinical presentation by tourist travelers, compared with the travelers visiting friends and relatives (who have limited insurance).

Other design considerations include the acquisition of diseases, such as malaria, which are primarily related to the destination rather than the reason for travel. Analysis of travel to regions of West Africa and East and southern Africa would have been more reflective of actual risk than reasons for travel. There is evidence that travelers visiting friends and relatives are overrepresented as travelers [4] to both Asia and sub-Saharan Africa, and the relative high proportion of disease prevalence in the group may be a reflection of greater exposure to and not increased likelihood of disease. The differing pattern of morbidity among the groups of travelers and immigrants visiting friends and relatives may relate to their economic status, access to and use of services, and medical care-seeking behavior, rather than to travel-associated risk.

All of these factors combined are design issues that we believe makes studies like the Leder et al. [1] study difficult to extend.